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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/435,274 | 11/05/1999 | VITALY H. CITOVSKY | 001.00301 | 4987 |

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| EXAMINER | |
|---|---|
| LAMBERTSON, DAVID A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/435,274 | CITOVSKY ET AL. | |
| | Examiner | Art Unit | |
| | David A. Lambertson | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-10 and 33-37* is/are allowed.

6)☒ Claim(s) *11-16,18-24 and 26-32* is/are rejected.

7)☒ Claim(s) *17 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 22, 2003 has been entered.

Claims 1-37 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed January 14, 2003, that is not addressed in this action has been withdrawn.

The declaration filed under 37 CFR 1.131 is acknowledged.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-15, 18, 19, 21-23, 26, 27 and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bujard *et al.* (US 5,654,168; see entire document; henceforth Bujard).

This rejection is predicated on the fact that the Tet repressor is a prokaryotic transcription factor, where there is no distinct evidence or apparent need for the repressor to have a nuclear localization signal. Therefore, when the Tet repressor is present in a fusion protein with an activation domain that does not have a known nuclear localization sequence (such as *GAL4*), the fusion protein is not believed to contain a nuclear localization signal in the absence of a third exogenous protein sequence containing such an element.

Bujard teaches a chimeric transcription factor comprising three elements: a DNA binding domain, a transcriptional activation domain, and a nuclear localization signal (see for example column 2, lines 46-51 and column 3, lines 29-39). The first part of the fusion polypeptide is comprised of a Tet repressor, which has the capacity to bind to the Tet operator sequence (see for example column 642-44 and column 8, lines 32-34). The second part of the fusion protein is a polypeptide that can directly or indirectly activate transcription (see for example column 9, lines 29-54), including such protein domains as the activation domain of *GAL4* (see for example column 10, lines 14-17). Bujard also teaches that, in addition to these two domains, a third domain for promoting transport of the fusion protein into the cell nucleus is used, such as a nuclear localization signal (see for example column 11, 4-16). The expression of the fusion protein can be driven from an expression vector by any one of a number of promoter elements (see for example 11, line 58 to column 12, line 1), which can be changed based on the particular host cell used (see for example column 11, lines 54-57). Bujard teaches the expression of this fusion protein in a variety of host cells, which include both mammalian and non-mammalian eukaryotic cells such as yeast (see for example column 13, line 65 to column 14, line 16). Bujard additionally teaches the presence of an operator sequence (that can functionally bind the

fusion protein; i.e., the Tet operator sequence) operatively linked gene of interest (see for example the Abstract, column 16, line 60-61, and column 18, lines 47-48). In a specific example, the gene of interest is *lac*Z or *lac*I or *gal*K, which are selectable marker genes (see for example column 32, lines 36-45). Bujard further contemplates the presence of these elements in a kit (see for example column 4, lines 49-53). Therefore, it is submitted that Bujard teaches all of the elements of the above-indicated claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard (as set forth above in the rejection if claims 11-15, 18, 19, 21-23, 26, 27 and 29-32 under 35 USC § 102(b)) in view of Pausch *et al.* (US 5,691,188; see entire document; henceforth Pausch).

Bujard teaches all of the elements set forth above in the rejection under 35 USC 102(b). However, Bujard does not specifically teach the use of *HIS3* as a selectable marker for detecting the activity of their fusion protein.

Pausch teaches the interchangeable use of any one of a variety of marker genes in a detection system, where the marker genes can be selected from *HIS3*, G418r, *URA3*, *LYS2*, *CAN1*, and *lac*Z (see for example column 9, lines 2-5).

It would have been obvious to substitute the *HIS3* marker for the markers used in the assay taught by Bujard (i.e., *lacZ*) because Pausch indicates that the *HIS3* and *lacZ* markers are interchangeable for detecting an activity. The ordinary skilled artisan would have been motivated to substitute the *HIS3* marker gene for the *lacZ* marker used by Bujard in order to increase the number of selectable markers that could be used in the detection system, thereby increasing the effectiveness of the assay system. Additionally, the *HIS3* marker gene is a native marker gene for yeast systems, thereby improving the detection system when the assay is performed in yeast cells, as suggested by Bujard. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when substituting the *HIS3* marker gene for the *lacZ* marker gene explicitly disclosed by Bujard.

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Claims 20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard (as set forth above in the rejection if claims 11-15, 18, 19, 21-23, 26, 27 and 29-32 under 35 USC § 102(b)) in view of Yabusaki *et al.* (US 5,137,822; see entire document; henceforth Yabusaki).

Bujard teaches all of the elements set forth above in the rejection under 35 USC 102(b). However, Bujard does not specifically teach the use of the *ADH1* promoter to drive the expression of the chimeric fusion protein in their assay.

Yabusaki teaches that the *ADH1* promoter can be used for achieving high levels of expression in yeast cells (see for example column 2, lines 1-5).

It would be obvious to the ordinary skilled artisan to combine the teachings of Yabusaki with those of Bujard because the inventions both involve the expression of proteins in yeast cells, and Bujard suggests substituting promoter elements based on their appropriateness in particular

host cells. The ordinary skilled artisan would have been motivated to substitute the *ADH1* promoter from Yabusaki for the promoters used in Bujard because, as Yabusaki teaches, the *ADH1* promoter is good for obtaining high levels of expression in yeast. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when substituting the *ADH1* promoter of Yabusaki for the promoters used by Bujard.

***Allowable Subject Matter***

Claims 1-10 and 33-37 are allowed.

Claims 17 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER